Exercise Testing in Cystic Fibrosis: Who and Why?

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ABSTRACT:

Annual review exercise testing is recommended by the Cystic Fibrosis (CF) Trust. Testing to date has focused on evaluating aerobic fitness, a key prognostic indicator. Tests available range from simple field tests, to comprehensive evaluations of aerobic exercise (dys)function – cardiopulmonary exercise testing (CPET).

'Field tests', although easy to perform are limited in the information they provide. Whereas CPET, the 'gold standard' measure of aerobic fitness, is recommended as the first choice exercise test by the European CF Society Exercise Working Group. CPET offers a precise cardiovascular, respiratory and metabolic evaluation of exercise capacity, including assessment of mechanism(s) of exercise limitation.

(100 words)

LIST OF ABBREVIATIONS:

CF = Cystic Fibrosis

CPET = Cardiopulmonary Exercise Test

FEV_1 = Forced expiratory volume in 1 second

HR = Heart Rate

SpO_2 = Oxygen saturations measured by pulse oximetry

$\dot{V}O_2$ = Oxygen Uptake

$\dot{V}CO_2$ = Carbon Dioxide elimination

$\dot{V}_E$ = Minute ventilation

V_D = Lung dead space

MVV = Maximal voluntary ventilation

AT = Anaerobic threshold

$\dot{V}O_2/HR$ = Oxygen extraction per heart beat – the 'Oxygen Pulse'

INTRODUCTION:

Exercise is an important therapeutic modality for individuals with cystic fibrosis (CF), with higher physical activity levels being associated with greater aerobic fitness,[1] pulmonary function [forced expiratory volume in 1 second (FEV_1)],[1] glycaemic control,[2] and bone mineral density.[3] Furthermore, exercise training programmes in individuals with CF may slow the decline in FEV_1,[4] and improve lung function,[5,6] exercise capacity,[6] and quality of life.[7] Exercise is also shown to enhance mucociliary clearance.[8] Importantly, exercise capacity is of prognostic significance for CF, with several studies demonstrating that better aerobic fitness [maximal oxygen uptake ($\dot{V}O_2max$)] is associated with greater 7-12 year survival.[9-11]

Exercise physiology – The Basics

In order to understand data generated from clinical exercise testing, a basic understanding of exercise physiology is required. Inadequate training in supervision and interpretation are cited as reasons why ≤10% of UK CF centres perform `gold standard` cardiopulmonary exercise testing (CPET).[12]

Energy generation is facilitated by the metabolism of carbohydrate and/or lipid substrates by aerobic (in presence of O_2) or anaerobic (in absence of O_2) processes in order to generate adenosine triphosphate - the energy source which allows muscles to contract. Such reactions produce differing amounts of carbon dioxide (CO_2) that requires exhalation.

During incremental exercise, $\dot{V}O_2$ increases linearly with workload until peak $\dot{V}O_2$ is attained. In some but not all cases, a plateau will be reached where despite further increases in workload, $\dot{V}O_2$ can increase no further - termed $\dot{V}O_2$ max. All individuals have a ceiling for

how much exercise can be performed. Physiologically, we are halted by one of the following three mechanisms - ventilatory ability to supply O_2, circulatory ability to deliver O_2 to and remove CO_2 from exercising muscles, or muscular extraction and utilisation of O_2 for energy conversion. Motivation may also contribute (See Figure 1 for overview).

Typical exercise response:

During exercise, breathing patterns adapt to meet energy needs with initial increases in tidal volume (V_T) and, later, changes in respiratory rate occurring to match demands for $\dot{V}O_2$ and CO_2 elimination ($\dot{V}CO_2$). Minute ventilation ($\dot{V}_E$) may increase as much as 25-fold with exercise, and healthy individuals reach their $\dot{V}O_{2peak}$ at a $\dot{V}_E$ max that is short of their maximal voluntary ventilation (MVV), with significant ventilatory reserve evident at peak exercise.

Cardiac output is also increased with exercise since both heart rate (HR) and stroke volume (SV) increase. Most healthy children have cardiac limitation at maximal exercise, reaching HR_{peak} during CPET. At the muscular level, fatigability and metabolism may also contribute to exercise limitation. Deconditioning causes reductions in muscular capillary numbers (impaired O_2 transfer in exercising muscle), mitochondrial density (impaired O_2 utilisation in muscle) and oxidative enzyme concentrations (impaired energy transformation in muscle). Thus, a deconditioned individual has less capacity for, and a shorter duration of, oxidative energy metabolism, with an earlier switch to anaerobic metabolism [anaerobic threshold (AT)]. This in turn results in accumulation of fatigue-related metabolites and consequently reduces exercise tolerance.

Exercise physiology – What might be different in CF?

Individuals with CF may have exercise capacity that is similar or greater than many healthy individuals, despite some having significantly lower ventilatory reserve at maximal exercise. High exercise capacity is especially seen in young children and adolescents with CF who are physically active with good lung function. Ventilatory limitation is often not a primary limiting factor during exercise in these children, where similar $\dot{V}O_{2peak}$ levels to their healthy peers may be recorded. However, some individuals with CF do experience significant impairment to exercise capacity due to factors including ventilatory limitation, cardiac and/or muscular factors, or commonly physical deconditioning which is at least partially remediable with a training programme.

As lung disease severity progresses, ventilatory limitation during exercise is common, with $\dot{V}_{Emax}$ often reached at much lower workloads and $\dot{V}O_2$. Individuals with CF may present with increased lung dead space ($\dot{V}_D$) that worsens with lung disease severity, and which can be increased during exercise, with higher $\dot{V}_E$ needed to achieve similar $\dot{V}O_2$. Additionally, airway obstruction due to mucus within the airways (+/- airway hyper-reactivity) may occur in CF, requiring greater inspiratory airflows to be generated with greater respiratory muscle effort needed to achieve similar ventilation. In contrast to healthy individuals who have significant ventilatory reserve at maximal exercise, a person with CF may have an exercise $\dot{V}_{E\,max}$ that reaches or even exceeds predicted MVV.[13] In short, those with more severe CF may have higher metabolic demands during exercise due to increased work of breathing, as well as a higher $\dot{V}_{Emax}$, due to increasing physiological $\dot{V}_D$. Such factors, coupled with inability to increase V_E due to lung disease contribute to ventilatory limitation being the principal factor determining exercise capacity in these individuals.

Cardiac disease and age each affect HR and SV and may limit exercise. Oxygen delivery can be investigated during CPET and cardiac (dys)function identified. O_2 pulse ($\dot{V}O_2$/HR) measures O_2 extraction per heart beat and estimates SV. This is important in CF, since some individuals are exercise-limited by an inability to sufficiently increase SV.

Muscle-related factors may also play a role in people with CF. Importantly, non-pathophysiological physical deconditioning may be present. Given the prognostic importance of exercise capacity, this may be seen as an important early warning sign for intervention.

It is important to note that much of the value of CPET is that it demonstrates the integration of the cardiovascular, pulmonary and muscular systems during exercise. Indeed, many CPET tests in CF youth serve to illustrate the capacity for compensation e.g. attaining functionally 'normal' exercise capacity despite having to physiologically compensate for ventilatory or other dysfunction.

Exercise testing in CF

Why test?

Exercise is a key component of CF management with annual review exercise testing is recommended by the CF Trust.[14] Exercise testing allows a functional measure of exercise performance. Exercise evaluations facilitates assessment of interval changes in clinical status, and are of prognostic significance,[9-11] such that tests identifying poor exercise capacity for the degree of lung function deficit warrant prompt attention and act as an early warning of impending decline. Exercise testing is also utilised for transplant stratification.[15]

Undertaking an exercise test may itself have an empowering effect on the individual testee, with the demonstration that exercise can often be performed to a high-intensity freeing a participant from personal uncertainty and/ or parental fears in future activities. Exercise test results can also facilitate exercise programmes tailored to the needs of each individual – e.g. improving fitness, or maintenance in those with significant ventilatory limitation but good fitness levels.

Furthermore, exercise testing has importance as an outcome measure in clinical trials, with $\dot{V}O_{2peak}$ a secondary outcome of the UK gene therapy study,[16] and primary outcome of a recently completed phase IV study of Orkambi® (VX15:809-112, Vertex Pharmaceuticals).

Which test?

Available tests of aerobic fitness range from `field` tests to comprehensive analyses of aerobic exercise (dys)function, e.g. CPET. Whilst anaerobic (e.g.Wingate) tests and evaluations of muscular fatigue/fitness are available, this review focuses on aerobic exercise testing.

Field Tests

Several tests have historically been used to measure aerobic fitness in clinical practice in CF, due to their relative ease and low cost. However, these are volitional and often submaximal tests, lacking precise outcome measures. Examples include the 6-minute walk test [17] (constant workload, non-externally paced, and submaximal for all but the sickest), the 3-minute step test [18] (constant workload, submaximal) and shuttle tests.[19] Although incremental and maximal for many, shuttle tests remain volitional, with no clear ascertainment of maximal effort and little insight into the mechanism(s) of exercise limitation. The commonly-used 15-level version of the 10m shuttle test is submaximal for around 30% of healthy individuals, as well as many older children and adults with CF.[20] Furthermore, HR_{peak} and Borg breathlessness scores achieved during shuttle testing in CF are lower than that those for CPET in the same individuals, suggesting greater effort expenditure on CPET.[21] Collectively, these limitations highlight the need for more precise and detailed exercise testing where possible.

CPET

The authors firmly support CPET as the test of choice for both children and adults with CF, in line with the European CF Society (ECFS) exercise working group recommendations.[22] Measurement of $\dot{V}O_{2peak}$ by CPET is regarded as the gold standard method to evaluate aerobic fitness. Cycle ergometry with breath-by-breath analysis of gas exchange and ventilation offers a comprehensive exercise assessment of ventilatory, circulatory, and metabolic parameters during various exercise intensities. Workload is progressively increased incrementally during CPET using a `step` or ramp protocol, such that exercise responses up to and including maximal exercise can be measured within 8-12 minutes. Key measures of interest include $\dot{V}O_{2peak}$, $\dot{V}O_2$ at the ventilatory AT, and $\dot{V}_{Emax}$ in addition to peak power output, change in O_2 saturation (SpO_2), time to exhaustion, and effort and breathlessness ratings. CPET allows evaluation of the mechanism(s) of exercise limitation.

The recommended protocol for individuals with CF aged >10 years[22] is cycle ergometry using the Godfrey incremental exercise protocol[23] with monitoring of SpO_2, pulmonary gas exchange, ventilation, and HR. The stepwise increments (10 to 25W/min) used are based on stature and target an 8-12 minute test duration. Continuous ramp protocols are advocated by some, since the increments increase continuously similar to physiological responses.[24] Cycle ergometry with pulse oximetry only (but no gas exchange measures), or treadmill exercise tests are recommended as second best options.[22] The modified Bruce protocol is recommended for treadmill testing.

The main limitations to undertaking CPET are equipment costs and operator expertise, however in our opinion the value of the information provided justifies the need to invest in equipment and skills training. CPET tests generate a large dataset usually displayed in a series of graphs, known as the 9-panel plot (see Figures 2 and 3), which are used to measure or estimate key exercise parameters including $\dot{V}O_2$, $\dot{V}_{Emax}$, and the AT.

After checking data quality, one should first review $\dot{V}O_{2peak}$ and maximum workload to assess whether they are normal relative to appropriate (age, sex, and ethnicity) normative reference data. In addition, it is important to consider whether maximum effort has been reached with respect to HR_{peak}, respiratory exchange ratio at peak exercise and whether or not $\dot{V}O_2$ has plateaued at the end of exercise. If maximal exercise endpoints are unclear, supramaximal exercise testing to verify $\dot{V}O_{2\ peak}$ can be considered.[24] An abnormally low exercise capacity is defined as $\dot{V}O_{2peak}$ <80% predicted. The next challenge is to identify whether reduced $\dot{V}O_{2peak}$ may be due to cardiovascular and/or peripheral muscle disease, or as is more likely in more severe CF, the result of deconditioning and/or ventilatory limitation (Figure 1).

The normal mechanism for exercise termination in a healthy individual is cardiac limitation, with HR_{peak} being attained (no cardiac reserve) and $\dot{V}_E$ falling short of estimated MVV i.e. gas in the tank at the end of exercise – exercise $\dot{V}_E$ < 85% MVV.[22] The physiology in children differs from adults, and expected HR_{peak} falls with age, whilst children with CF often achieve a HR_{max} >200 beats/min during CPET.

AT onset provides a submaximal indicator of an individual's aerobic fitness. Deconditioning results in an early onset AT, indicative of reduced efficiency to transfer and utilise O_2 at the muscular level. An AT occurring < 50% predicted $\dot{V}O_{2max}$ (in the absence of cardiac disease or muscle abnormalities) is likely to be associated with deconditioning, and can be improved with training.

Who to test?

It is recommended that CPET has a role in providing guidance on prognosis and allowing individualised exercise counselling in CF from 10 years of age.[22] This age is recommended as a guide for those undertaking CPET using a cycle ergometer, since the participants are required to maintain cadence when pedalling, which some children find difficult, in addition to reaching the pedals (minimum height ~ 128 cm in our exercise laboratories), though technically acceptable tests can be achieved in younger children. It may be that ergometer tests in younger children can be attempted to familiarise them with procedures as well as providing motivation and guidance for exercise participation; and treadmill tests may also be performed in younger children (with or without a safety harness). A recently published review for this journal offers advice on how to perform, interpret and use CPET to guide exercise counselling in children with CF.[25]

When to test?

Interval CPET testing is recommended for children and adults with CF.[22] In our centres we recommend that annual CPET is undertaken as part of annual review. In addition, exercise testing plays a vital role in pre-transplant assessment, with both 6MWT and CPET[14] being validated for this purpose. Exercise testing before and after significant change or intervention is recommended, e.g. before/after the institution of Ivacaftor[26] or Orkambi®.

CASE EXAMPLE:

Patient A (FEV_1 95%pred), male (p.Phe508del/p.Ala457Pro, c.1369G>C) and aged 13 years attended for CPET at annual review. He attained $\dot{V}O_{2peak}$ of 38.7mL/kg/min (84% predicted), and HR_{peak} 184 beats/min. He had significant breathing reserve at peak exercise ($\dot{V}_{Emax}$ 77L/min versus calculated MVV 108L/min), and had $\dot{V}O_2$ at AT of 40%pred $\dot{V}O_{2max}$. CPET suggested suboptimal exercise capacity, with deconditioning suggested by early onset of AT. Selected data from panels 3,4, and 5 of his 9-panel plot are displayed (Figure 2).

An action plan was made by physiotherapy colleagues who devised an individualised exercise programme. Improvements in both exercise capacity and physical conditioning were evident upon retesting 5 months later (Figure 3). $\dot{V}O_{2peak}$ was 43.2mL/kg/min (96% predicted), and $\dot{V}O_2$ at AT had improved to 48%pred $\dot{V}O_{2max}$. An identical HR_{peak} and similar breathing reserve were recorded.

CONCLUSIONS

Traditional testing of lung health using spirometry tells us how much and how fast air exits the lungs. Measurement of efficiency and performance of these lungs in combination with cardiovascular, pulmonary and musculoskeletal systems during exercise (CPET) provides precise information that is of prognostic importance, as well as allowing us to further understand individual pathophysiology of exercise limitation and individually tailor exercise programmes for young people with CF.

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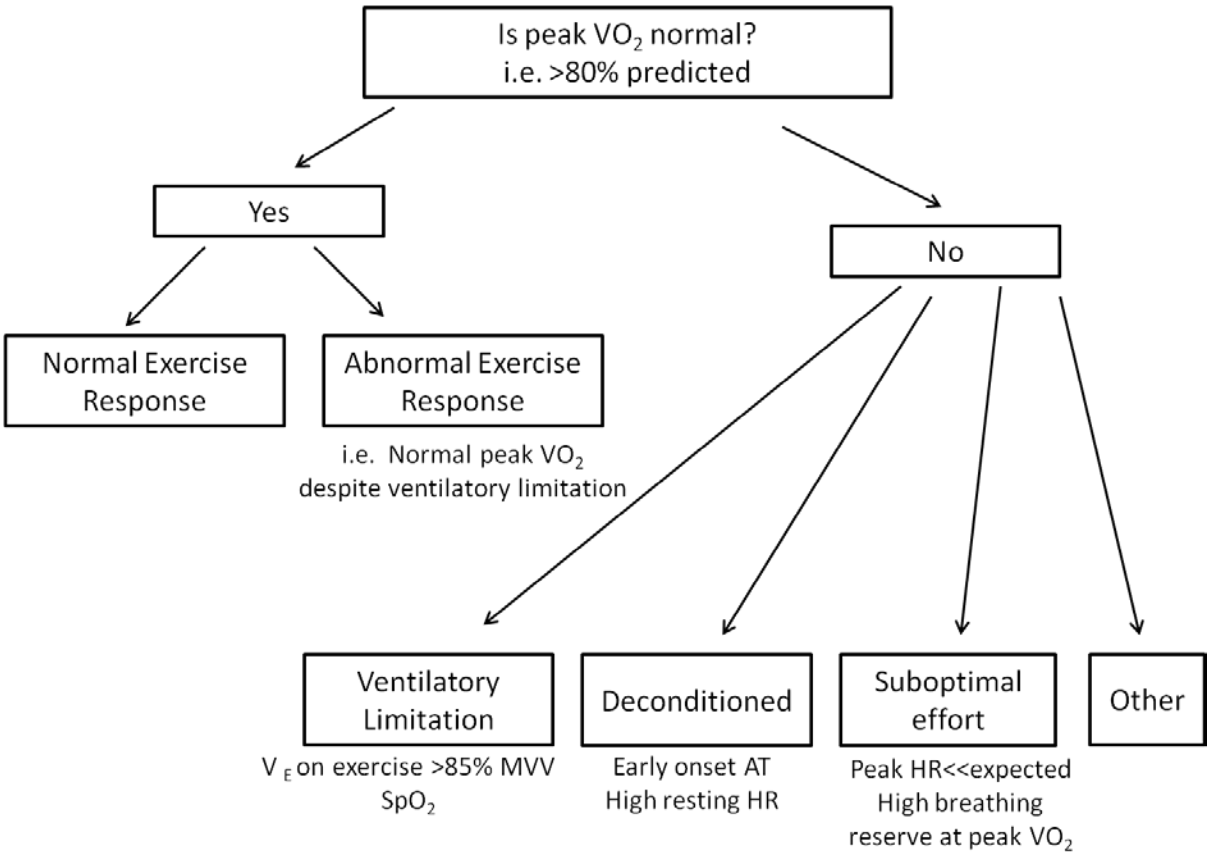
Figure 1

Schematic overview of how to determine exercise function and/or cause of any dysfunction in individuals with CF



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Urquhart and Vendrusculo, *Paediatr Respir Rev* 2017;**24:**72-78.[21]

Figure 2

Case example illustrating an exercise-limited and deconditioned CF patient (Selected data (Panels 3,4,5 shown) from CPET are displayed)

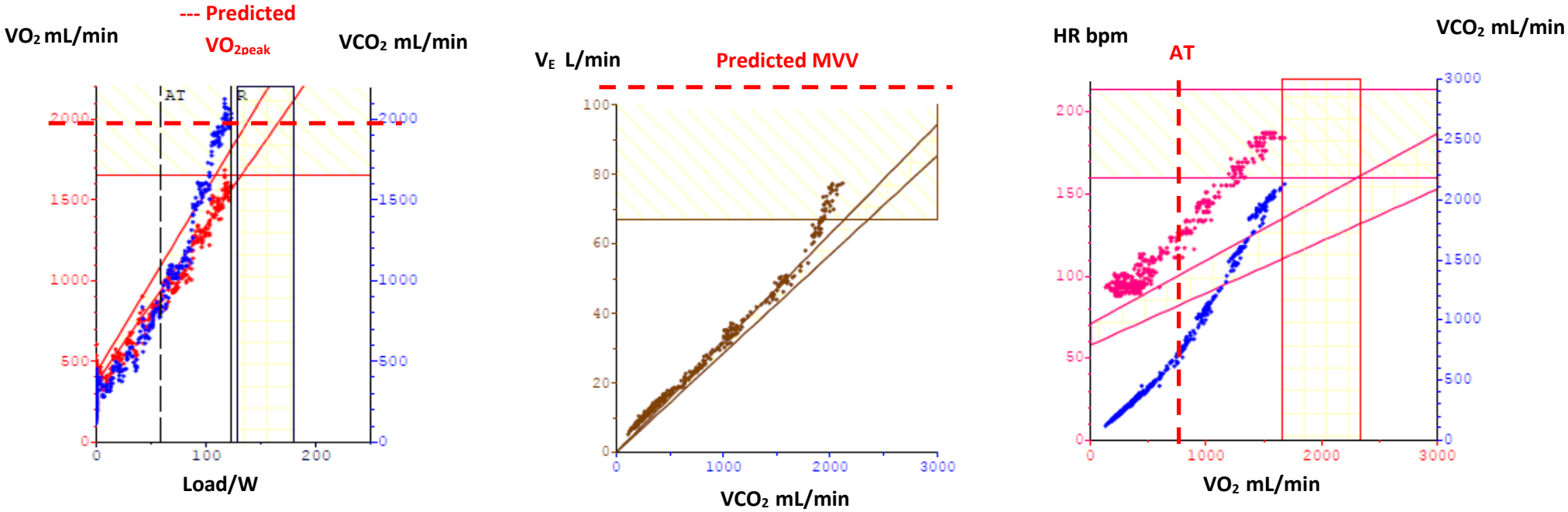

Figure 3

Improvements in exercise capacity and AT in same patient following individualised exercise programme

(Selected data (Panels 3,4,5 shown) from CPET are displayed)